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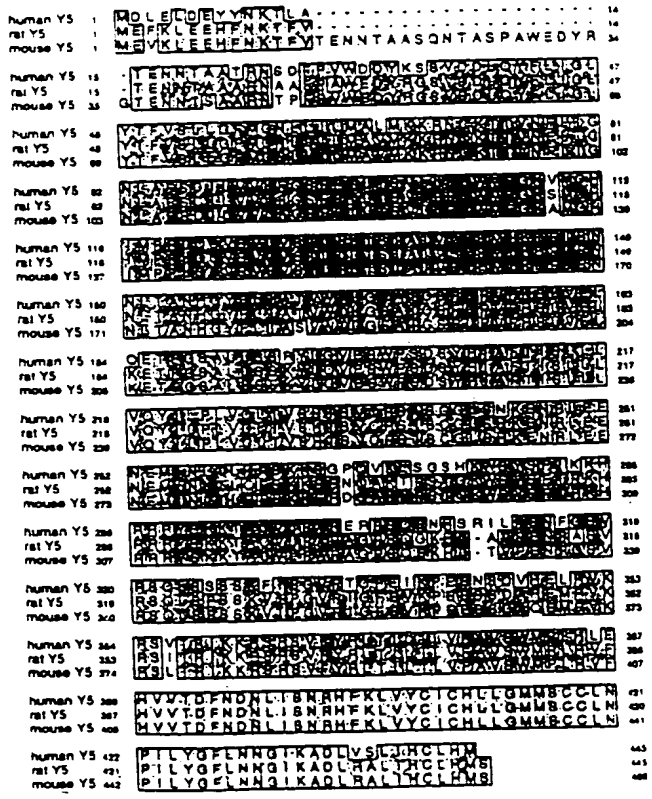
(54) Title: NEUROPEPTIDE Y-Y5 RECEPTOR

(57) Abstract

The invention provices isolated DNA molecules encoding the human, mouse and rat NPY-Y5 receptors. These isolated DNA molecules can be used to express the NPY-Y5 receptors in cells which can then be used to screen compounds for NPY agonist and antagonist activity.



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# NEUROPEPTIDE Y-Y5 RECEPTOR

The present invention relates to isolated DNA molecules which encode the neuropeptide Y-Y5 receptor. In addition the present invention relates to the use of these molecules in the production of the neuropeptide Y-Y5 receptor using recombinant technology and to methods of screening and testing compounds for neuropeptide Y (NPY) agonist or antagonist activity.

In developed affluent countries the prevalence of obesity is alarming and it is now a massive contribution to morbidity and mortality in addition to being socially disadvantageous. Fat deposition in the abdominal area is a particular problem in relation to risk of Type II diabetes and cardiovascular disease. However, until recently, the molecular mechanisms controlling appetite, energy expenditure and adiposity have been surprisingly ill-understood.

Obesity has well-known associations with non-insulin-dependent diabetes (NIDDM), hypertension, dyslipidaemia and coronary heart disease, as well as less obvious links with diseases such as osteoarthritis and various malignancies; it also causes considerable problems through reduced mobility and decreased quality of life. Seven forms of rodent obesities, determined by single gene mutations, have been identified: yellow [*Ay*], adipose [*Ad*], diabetes [*db*], fat [*fat*], tubby [*tub*] and obese [*ob*] in the mouse and fatty [*fa*] in the rat. The obese phenotypes caused by these mutations differ in their age of onset, severity and the degree of insulin resistance. Similar phenotypes can also be seen in obese humans. Recently the molecular bases for some of these mutations has been elucidated. Of these the [ob] gene product "leptin" has created the most interest. However, many other factors are also involved in regulating energy balance and body fat distribution. Four factors appear most likely to have an important role: these are neuropeptide Y (NPY), corticotropin releasing factor (CRF)/ACTH/glucocorticoids, insulin and galanin. In particular, NPY and its receptors play an important role in the regulation of appetite and in a related manner, obesity.

Neuropeptide Y (NPY) forms a family (called the pancreatic polypeptide family) together with pancreatic polypeptide (PP) and peptide YY(PYY), which all consist of 36 amino acids and possess a common tertiary

structure. Neuropeptide Y (NPY) receptors, members of the G protein-coupled receptor superfamily, are activated by one of the most abundant peptides in the mammalian nervous system and subsequently influence a diverse range of important physiological parameters, including effects on psychomotor activity, central endocrine secretion, anxiety, reproduction, vasoactive effects on the cardiovascular system and most importantly, potent effects on appetite. A number of neuropeptides and classical neurotransmitters, including noradrenaline and serotonin, modulate ingestive behaviours. However, NPY stands out from the many neurotransmitters with experimental effects on food intake in being able to induce obesity. Injections of NPY into the paraventricular nucleus (PVN), have been shown to increase, in a dose dependent manner, feeding and drinking behaviour in the rat. A single injection of NPY can increase food intake several-fold for several hours and is effective even during the light phase when rats usually eat little, and in animals that have already eaten to satiety. Consequently, NPY peptides are certainly among the most potent orexygenic substances known in either food deprived or satiated animals. Repeated NPY injections into the PVN result in a massive and persistent feeding response and the rats ultimately develop obesity, with a true increase in body fat content. The importance of NPY as a mediator of appetite/obesity regulation is further enhanced by the very recent report that the obese gene product leptin inhibits NPY synthesis and release.

Injections of NPY into the paraventricular nucleus cause a prompt and robust increase in plasma ACTH levels and there is clear evidence that NPY-induced ACTH secretion is mediated by corticotropin releasing factor (CRF). However, its mode of action as well as its interaction with CRF within the brain is largely unknown, as are its interrelationships with other hormones, such as insulin. Nevertheless an agent which increases appetite and raises glucocorticoid levels might be important in generating central obesity.

Specific agonists and antagonists of NPY are therefore likely to be of substantial benefit for therapy of a wide range of clinical disorders. As NPY possess a compact tertiary structure and different parts of the molecule are required for interaction with different subtypes of the receptor, the logical developments of both agonists and antagonists is critically dependent upon the availability and knowledge of specific receptor structure.

It is presently known that NPY binds specifically to at least five receptors; Y1, Y2, Y3, Y4 and Y1-like (or "atypical Y1"). While it has been demonstrated that NPY receptors couple to the adenylate cyclase second messenger system, it remains probable that additional NPY receptor subtypes exist since there is evidence that phosphatidylinositol turnover, cations, and arachidonic acid may also function as second messengers for NPY.

Since NPY agonists and antagonists may have commercial value as, for example, potential anti-hypertensive agents, cardiovascular drugs, neuronal growth factors, anti-psychotics, anti-obesity and anti-diabetic agents, the ability to produce NPY receptors by recombinant DNA technology would be advantageous. To this end, DNA molecules encoding Y1, Y2, Y3 and Y4 have previously been isolated.

The present inventors have now isolated novel DNA molecules encoding the human, mouse and rat Y1-like (hereinafter referred to as NPY-Y5) receptors. Similar DNA molecules encoding human and rat NPY-Y5 have been described in International (PCT) Patent Specification No. WO 96/16542, however, these encode receptors with, in the case of the human NPY-Y5, an additional 10 N-terminus amino acids, and, in the case of the rat NPY-Y5, an additional 11 N-terminus amino acids. Through analysis of several cDNA clones and RT-PCR using specific primers for intron and exon sequences, the present inventors have confirmed that the human, mouse and rat NPY-Y5 receptor does not include these additional 10/11 amino acids. The DNA molecules described in WO 96/16542 may thus exhibit lower expression rates over those of the present invention. In addition, the receptors encoded by the DNA molecules described in WO 96/16542, may show lower and possibly altered activity.

Thus, in a first aspect, the present invention provides an isolated DNA molecule encoding an NPY-Y5 receptor having about 445 amino acids or a functionally equivalent fragment thereof.

Preferably, the isolated DNA molecule encodes an human, mouse or rat NPY-Y5 receptor.

Most preferably, the isolated DNA molecule has a nucleotide sequence substantially corresponding or, at least, >80% (more preferably, >95%) homologous to that shown:

(i) at nucleotides 6291 to 7625 of Figure 1.

(ii) at nucleotides 63 to 1397 of Figure 2,
(iii) at nucleotides 115 to 1449 of Figure 3, or
(iv) at nucleotides 73 to 1470 of Figure 4.

The isolated DNA molecule may be incorporated into plasmids or expression vectors, which may then be introduced into suitable bacterial, yeast and mammalian host cells. Such host cells may be used to express the NPY-Y5 receptor encoded by the isolated DNA molecule.

Accordingly, in a second aspect, the present invention provides a mammalian, yeast or bacterial host cell transformed with the DNA molecule of the first aspect.

In a third aspect, the present invention provides a method of producing NPY-Y5 receptors comprising culturing the host cell of the second aspect under conditions enabling the expression of the DNA molecule and optionally recovering the NPY-Y5 receptor.

Preferably, the host cell is mammalian or bacterial. Where the cell is mammalian, it is presently preferred that it be a Chinese hamster ovary (CHO) cell, human embryonic kidney 293 cell or insect Sf9 cells.

In a preferred embodiment, the NPY-Y5 receptor is expressed onto the surface of the host cell.

The DNA molecules of the present invention represent a NPY receptor which may be of interest both clinically and commercially as it is expressed in many regions of the body and NPY affects a wide number of systems.

By using the nucleic acid molecules of the present invention it is possible to obtain neuropeptide Y-Y5 receptor protein in a substantially pure form.

Accordingly, in a fourth aspect, the present invention provides NPY-Y5 receptor in a substantially pure form.

Preferably, the purified NPY-Y5 has an amino acid sequence substantially corresponding to any one of the amino acid sequences shown in Figure 5.

In a fifth aspect, the present invention provides an antibody capable of specifically binding to an NPY-Y5 receptor.

In a sixth aspect, the present invention provides a non-human animal transformed with a DNA molecule according to the first aspect of the present invention.

In a seventh aspect, the present invention provides a method for detecting agonist or antagonist agents of NPY-Y5 receptor, comprising contacting a NPY-Y5 receptor or a cell transfected with and expressing the DNA molecule of the first aspect with a test agent under conditions enabling the activation of a NPY-Y5 receptor, and detecting an increase or decrease in NPY-Y5 receptor activity.

In a further aspect, the present invention provides a nucleic acid probe comprising a nucleotide sequence of 10 or more nucleotides capable of specifically hybridising to a unique sequence within the DNA molecule of the first aspect.

In a still further aspect, the present invention provides an antisense nucleic acid molecule comprising a nucleotide sequence capable of specifically hybridising to an mRNA molecule which encodes NPY-Y5 receptor so as to prevent translation of the mRNA molecule. Such antisense nucleic acid molecules may include a ribozyme region to catalytically inactivate mRNA to which it is hybridised.

The term "substantially corresponding" as used herein in relation to the nucleotide sequences shown in Figures 1 and 2 is intended to encompass minor variations in the nucleotide sequence which due to degeneracy in the DNA code do not result in a change in the encoded protein. Further, this term is intended to encompass other minor variations in the sequence which may be required to enhance expression in a particular system but in which the variations do not result in a decrease in biological activity of the encoded protein.

The term "substantially corresponding" as used herein in relation to amino acid sequences is intended to encompass minor variations in the amino acid sequences which do not result in a decrease in biological activity of the NPY-Y5 receptor. These variations may include conservative amino acid substitutions. The substitutions envisaged are:-

G, A, V, I, L, M; D, E; N, Q; S, T; K, R, H; F, Y, W, H; and P, Nα-alkalamino acids.

The invention is hereinafter described by way of the following non-limiting example and further, with reference to the accompanying figures.

**Brief description of the Figures**:

Figure 1 provides the nucleotide sequence of a genomic DNA molecule encoding the human NPY-Y5 receptor and includes the predicted amino acid sequence.

Figure 2 provides the nucleotide sequence of a cDNA encoding the human NPY-Y5 receptor and includes the predicted amino acid sequence.

Figure 3 provides the nucleotide sequence of a cDNA encoding the rat NPY-Y5 receptor and includes the predicted amino acid sequence.

Figure 4 provides the nucleotide sequence of a genomic DNA encoding the mouse NPY-Y5 receptor and includes the predicted amino acid sequence.

Figure 5 shows the degree of identity between the predicted amino acid sequence of the human, mouse and rat NPY-Y5 receptor proteins.

Figure 6a-f provide graphical results of binding assays conducted with CHO cells expressing NPY-Y5, Y5 ligands assayed were NPY, Leu 31 Pro 34 NPY, PP, PYY, NPY 2-36 and PYY 13-36.

Figure 7 provides graphical results of cAMP assays conducted on CHO cells expressing NPY-Y5 using the ligands NPY, Leu 31 Pro 34 NPY, PP, PYY and NPY 2-36.

**Example:**

EXPERIMENTAL PROCEDURES

**cDNA and Genomic Library Screening**

A human genomic P1 DNA library (Genome-Systems), a human foetal brain cDNA library (P. Seeburg, University of Heidelberg) and a rat hypothalamic cDNA library (Stratagene) were screened with a 632 bp $^{32}$P-labelled *EcoRI/Pst*1 fragment flanking exon 1C of the human NPY-Y1 gene. Hybridisation with the probe was performed in a solution containing 6xSSC,

5xDenhardt's solution, 0.1 % SDS and 100mg/ml denatured and sheared salmon sperm DNA at 60 °C for 16 h. Filters were washed twice for 15 min in 2xSSC/0.1 %SDS at 60 °C followed by a 15 min wash in 0.1xSSC/0.1% SDS and exposed to X-ray film (Kodak, X-Omat) using an intensifying screen at -70 °C for 16h. P1 DNA from positive clones was isolated according to the manufacturer's protocol. The DNA was digested with *Eco*RI, *Hind*III, *Bam*HI and *PstI* then subcloned into the Bluescript SK vector (Stratagene) generating clones covering all of the human Y1 and Y5 genes.

**Nucleotide Sequence Determination.**

Supercoiled plasmid DNA was alkaline-denatured and sequenced by the dideoxy chain termination method using T7 polymerase (Promega) (Sambrook *et al.*, 1992). The oligonucleotide primers used initially were complementary to the flanking region of the vector and then based on sequences obtained in order to complete the sequence analysis.

**Restriction Map Determination.**

P1 DNA was digested with restriction enzymes *Eco*RI, *Bam*HI, *Hind*III, alone and in all possible combinations, electrophoresed on a 0.8 % agarose gel, alkaline-denatured (0.4 M NaOH), capillary-transferred using 0.4 M NaOH to Hybond $N^+$ membranes and hybridised with several specific oligonucleotides, cDNAs and genomic DNA fragments obtained from the subcloning.

***In Situ* Hybridisation Analyses**

Sense and antisense riboprobes to the human NPY-Y5 receptor were synthesised using the DIG RNA Labelling Kit (SP6/T7) (Boehringer Mannheim). cDNA corresponding to the coding region of the human NPY-Y5 receptor was linearised and transcribed with either T7 (for antisense riboprobe) or SP6 (for sense riboprobe) RNA polymerase according to the manufacturers instructions using digoxygenin labelled dUTP.

Postmortem brain tissue was obtained from a young adult male without neurological disease. Specific brain regions were dissected and fixed by immersion in formalin for 36 hours and then embedded in paraffin. 6 mm serial sections were collected on slides subbed in chrom alum and stored at 4°C until used. Sections were dewaxed in Histoclear (National

Diagnostics) for 5 min, rehydrated in 100%, 70% and 50% alcohol for 2 min each then washed in phosphate buffered saline (PBS) for 5 min.

Sections were pretreated for 10 min at room temperature with 5 mg/ml proteinase K (Boehringer Mannheim) in 50mM Tris, pH 7.5, 5 mM EDTA. Sections were then washed twice with 0.1M glycine (in PBS) for 2 min, once in PBS then incubated for 1 h at room temperature in hybridisation buffer: 2 x SSPE, 50% formamide, 5% dextran sulfate, 1 x Denhardt's reagent, 100mg/ml tRNA type X-SA (Sigma). Digoxigenin labelled riboprobes to sense and antisense DNA (500ng) in 75ul of hybridisation buffer were added to the sections and hybridised at 42°C for 18 h in a humidified environment using a Hybaid Omnislide PCR Thermal Cycler (Integrated Sciences). After hybridisation, sections were washed at room temperature in 2 x saline sodium citrate (SSC) buffer, 0.15M NaCl/0.015 M Na-citrate, pH 7.0 for 10 min, then 0.2 x SSC for 30 min followed by treatment with 20mg/ml RNase [Sigma], in 10mM Tris, pH 7.5, 15 mM NaCl for 15 min at room temperature. After RNase treatment the slides were washed in 2 x SSC for 5 min at room temperature then 0.2 x SSC at 37°C for 30 min.

Tissues were processed for immunological detection by washing for 10 min in buffer A (100mM Tris-HCl, pH 7.5, 150 mM NaCl), then incubated for 30 min with a 2% blocking solution (Boehringer Mannheim) with 0.3% Triton X-100 in buffer A. The sections were then incubated for 2 hours with an alkaline phosphatase-conjugated anti-digoxigenin antiserum (Boehringer Mannheim, diluted 1/500 in buffer A plus 0.5% blocking reagent), washed twice for 5 min each in buffer A followed by a wash in 100mM Tris-HCl, pH 9.5, 100mM NaCl, 50mM $MgCl_2$ for 2 min. The labelled probes were visualised using nitro blue tetrazolium and bromochloro-indoyl phosphate as substrates for 18 hours in the dark. Sections were washed for 10 min in 10mM Tris-HCl, pH 8.0, 1 mM EDTA, then 3 quick washes in distilled water, mounted with Aquamount [Gurr] and examined using a Zeiss Axiophot microscope with Nomarsky optics using a blue filter.

**Expression of NPY Y5**

The rat Y5 receptor protein was expressed as follows: the mammalian expression construct rpHz17 was made by subcloning a 1.9 kb fragment containing the whole coding region and almost the entire 3'

untranslated region of the rat NPY Y5 cDNA into the pPRC/CMV vector (Invitrogen). The construct is under the control of the CMV promoter and contains the neomycin gene for selection. The expression construct rpHz17 was transfected into mammalian cell lines CHO-K1 and HEK using a modified calcium phosphate transfection method.

**NPY-Y5 Binding Assay**

The coding region of the NPY-Y5 receptor was subcloned in the pRC/CMV expression vector and transfected into the chinese hamster ovary (CHO) K1 cell line by using a modified calcium phosphate transfection method. CHO cells were maintained under 5% $CO_2$ in Dulbecco's modified Eagles medium (DMEM)/Ham's F-12 medium (1:1) with 2mM glutamine and 10% fetal calf serum. Stably transfected cells were selected with neomycin and tested for the ability to bind NPY/PYY analogues. Transfected cells ($1x10^6$) were incubated in 0.5ml assay buffer [50mM Tris-HCl, pH 7.4, 2mM $CaCl_2$, 5mM KCl, 120mM NaCl, 1mM $MgCl_2$, 0.1% bovine serum albumin] in the presence of 0.05nM $^{125}I$ labeled NPY and increasing concentrations of human NPY and related peptides. Cells were incubated for 3 hours at 15°C then layered onto 0.5ml horse serum before being palleted in a microcentrifuge for 4 min. Radioactivity was measured for 1 min in a $\gamma$ counter. Results of binding assays involving CHO cells expressing NPY-Y5 receptor are shown in Table 1, expressed as a percentage of the maximal specifically bound radiolabeled NPY. Results are the pooled data from three separate binding curves with triplicate points.

TABLE 1

| Peptide | $IC_{50}$ (nM) Mean+/-SE |
|---|---|
| NPY | 7.2+/-0.2 |
| Leu31 Pro34 NPY | 7.3+/-0.3 |
| PP | 21+/-4.3 |
| PYY | 25+/-4 |
| NPY 2-36 | 27+/-3.4 |
| PYY 13-36 | > 1000 |

**cAMP Assays**

CHO cells expressing NPY-Y5 receptor were grown and maintained in Dulbecco's modified Eagles medium: Hams F12 medium (1:1 v/v) supplemented with 2mM L-glutamine and 10% (v/v) foetal calf serum at 37°C under an atmosphere of 10% $CO_2$ in humidified air in 150cm$^3$ flasks. Experiments were performed in 24 well cluster dishes when cells had reached confluence.

Inhibition of forskolin-stimulated [$^3$H]-cAMP accumulation

Cell monolayers were incubated for 2h at 37°C in 1ml/well of HEPES buffered Hanks solution (HBH; 20mM, pH 7.4) containing [$^3$H]-adenine (74kBq/well). Prior to the addition of agonist, cells were incubated in 1ml/well HBH containing the phosphodiesterase inhibitor Ro 20-1724 for 30min. Agonists (in 10µl HBH) were added to the assay system following the addition of forskolin (10µM) and the incubation continued for 10min. The temperature of the incubation medium was maintained at 37°C during these manipulations. Incubations were terminated by the addition of 50µl conc. HCl to each well which lysed the cells. [$^3$H]-cAMP content of the supernatant buffer from each well was isolated by sequential ion exclusion Dowex-alumina chromatography. After the addition of emulsifier scintillator (15ml), radioactivity was determined by liquid scintillation counting. Results are provided in Table 2.

TABLE 2

| Peptide | $IC_{50}$ Values (n=3) |
|---|---|
| NPY | 163.7±70.0nM |
| PYY | 45.1±31.4nM |
| PP | 73.4±47.4nM |
| [2-36]NPY | 242.5±171.4nM |
| $Leu^{31}Pro^{34}NPY$ | 75.9±38.3nM |

## RESULTS

### Identification of NPY-Y5 receptor gene

The cloning and characterisation of the 5' upstream region of the human NPY-Y1 receptor gene, while confirming the existence of several alternative 5' exons for the Y1 gene (Ball *et al.*, 1995), also revealed a region of extensive homology with G-protein coupled receptors in exon 1C, involving a partial open reading frame in the opposite orientation. Comparison of this 200 amino acid sequence, which contained parts of the third intracellular loop and transmembrane domains VI and VII, with the Genbank database, identified the human NPY-Y1 receptor as the closest related receptor with 37 % identity. Subcloning and sequencing of the entire 7kb area between exon 1C and exon 1B of the Y1 gene confirmed the presence of a gene encoding a novel NPY receptor subtype named Y5 (Figure 1). Screening of human fetal brain and rat hypothalamic cDNA libraries with a 632 bp human genomic Y5 fragment under high stringency identified full length cDNA clones for both species. These sequences encode a 445 amino acid long Y5 receptor (Figures 2 and 3). The human genomic sequence (Figure 1) shows two candidate initiator ATG codons, however analysis of several cDNA clones and RT-PCR using specific primers for intron and exon sequences has established that one of these ATG codons (located 30 nucleotides upstream of the other ATG) is located within an intron. The overall identity between the human and rat NPY-Y5 receptors after this correction is 89%. Figure 5 shows that the degree of identity between the predicted amino acid sequence of the human and rat NPY-Y5 receptors.

The exon which encodes the 5' untranslated region of the human Y5 gene is separated by a 2.7 kb intron from exon 2 and is located about 2.8kb upstream of exon 1B of the NPY-Y1 gene. The close proximity of these two 5' exons orientated in opposite directions suggests a possible co-regulation of transcription of both genes through a common promoter region.

An interesting feature of the human Y5 gene, however, is the harbouring of exon 1C of the NPY-Y1 gene within the coding region of the NPY-Y5 gene. The 100 bp long exon 1C encodes, in its opposite strand, a part of the Y5 sequence containing most of the third intracellular loop of the receptor protein. This cytoplasmic loop can vary significantly in size between G-protein coupled receptors and is thought to be involved in determination of

the specificity of coupling to different G-protein complexes. In contrast to all other known NPY receptor subtypes, this region in the Y5 receptor is unusually large, consisting of about 150 amino acids. In the corresponding region of the NPY-Y1 gene, shortly after the fifth transmembrane domain, a small 97 bp intron containing an in frame stop codon interrupts the coding region (Fig. 1) suggesting that this noncoding region has gained two additional functions after duplication. One is to encode part of the Y5 protein sequence and the other is to fulfil a regulatory function in tissue specific transcription, as an alternatively spliced 5' exon of the Y1 gene. Transcription activation of exon 1C certainly will have an effect on Y5 expression, most likely inhibiting mRNA production. However, such a mechanism may represent only one aspect of a regulatory interaction between these two receptor genes. The close proximity of exon 1B of the Y1 gene and exon 1 of the Y5 gene suggests an additional control mechanism(s) for the specific transcriptional activation of one or the other gene.

**Pharmacological characterisation of the Y5 receptor**

NPY binding analysis of CHO cell lines stably expressing the rat Y5 receptor subtype show a ligand specificity and rank order of potency (NPY = NPY > PYY[$Leu^{31}$,$Pro^{34}$] = NPY[2-36] = PP >> PYY[13-36] ) indicative of a NPY receptor with a Y1-like pharmacology, as well as responding strongly to the feeding specific ligand NPY[2-36] (Figure 6a-f). The same profile of selectivity for these different NPY analogues can be seen in the results obtained from experiments measuring the inhibition of adenylate cyclase activity (Figure 7).

***In situ* hybridisation analysis**

A comprehensive study was made of the distribution of the Y5 receptor mRNA in hypothalamic regions of the human hypothalamus. Hybridisation with a sense probe to Y5 showed no specific labelling, however, antisense probe showed extremely high expression of Y5 receptor mRNA is found in large neurons of the paraventricular nucleus. High levels are also found in the dorsomedial nucleus, supraoptic nucleus and in the mamillary body as well as in the midline thalamic nuclei. Within a nucleus the distribution was not always homogenous. For example in the dorsomedial region, clearly unlabelled large pyramidal neurons were found mingled with

labelled neurons, suggesting funtional specialisation. Preliminary results for the Y1 receptor suggest that the human NPY-Y1 receptor has a similar distribution to that of the Y5 receptor, however, with some identifiable differences supporting the theory of a co-regulatory transcription activation of the two genes.

**Expression of NPY-Y5**

The expressed Y5 receptor protein appears to have a unique distribution and relative affinities for different NPY/PYY/PP analogues. It is also expected that the Y5 receptor will be functionally unique, relative to other NPY receptors, and may be very important in, for example, the development of drugs for a number of conditions such as appetite/obesity disorders, hypertension, locomotor problems, memory loss, sleeping disorders, migraine and gastrointestinal (GI) and cardiovascular disorders.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

**References**:-

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2. Sambrook, J., Fritsch, E.F. & Maniatis, T. (1992). *Molecule cloning (A Laboratory Manual)* 2nd ed. (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York).

Claims:-

1. An isolated DNA molecule encoding a NPY-Y5 receptor having about 445 amino acids or a functionally equivalent fragment thereof.

2. An isolated DNA molecule according to claim 1, wherein said DNA molecule encodes a human, mouse or rat NPY-Y5 receptor.

3. An isolated DNA molecule according to claim 2, wherein the DNA molecule encodes a human NPY-Y5 receptor.

4. An isolated DNA molecule encoding an NPY-Y5 receptor, wherein the DNA molecule is at least 80% homologous to the nucleotide sequence shown:
(i) at nucleotides 6291 to 7625 in Figure 1.
(ii) at nucleotides 63 to 1397 in Figure 2,
(iii) at nucleotides 115 to 1449 in Figure 3, or
(iv) at nucleotides 73 to 1470 in Figure 4.

5. An isolated DNA molecule encoding an NPY-Y5 receptor, wherein the DNA molecule is at least 95% homologous to the nucleotide sequence shown:
(i) at nucleotides 6291 to 7625 in Figure 1.
(ii) at nucleotides 63 to 1397 in Figure 2,
(iii) at nucleotides 115 to 1449 in Figure 3, or
(iv) at nucleotides 73 to 1470 in Figure 4.

6. An isolated DNA molecule encoding an NPY-Y5 receptor, wherein said DNA molecule has a nucleotide sequence substantially corresponding to that shown at nucleotides 6291 to 7625 in Figure 1.

7. An isolated DNA molecule encoding a NPY-Y5 receptor, wherein the DNA molecule has a nucleotide sequence substantially corresponding to that shown at nucleotides 63 to 1397 in Figure 2.

8. An isolated DNA molecule encoding a NPY-Y5 receptor, wherein the DNA molecule has a nucleotide sequence substantially corresponding to that shown at nucleotides 115 to 1449 in Figure 3.

9. An isolated DNA molecule encoding a NPY-Y5 receptor, wherein the DNA molecule has a nucleotide sequence substantially corresponding to that shown at nucleotides 73 to 1470 in Figure 4.

10 A plasmid or expression vector including DNA molecule according to any one of the preceding claims.

11. A host cell transformed with the DNA molecule according to any one of claims 1 to 9.

12. A host cell according to claim 11, wherein the cell is a mammalian or bacterial cell.

13. A host cell according to claim 12, wherein the cell is a chinese hamster ovary (CHO) cell, human embryonic kidney (HEK) 293 cell or insect Sf9 cell.

14. A host cell according to any one of claims 11 to 13, wherein the cell expresses NPY-Y5 receptor onto the cell's surface.

15. NPY-Y5 receptor in a substantially pure form.

16. NPY-Y5 receptor according to claim 15, wherein said receptor consists of about 445 amino acids.

17. NPY-Y5 receptor according to claim 15 or 16, wherein the NPY-Y5 has an amino acid sequence substantially corresponding to any one of the amino acid sequences shown in Figure 5.

18. An antibody capable of specifically binding to a NPY-Y5 receptor according to any one of claims 15 to 17.

19. A non-human animal transformed with a DNA molecule according to any one claims 1 to 9.

20. A method for detecting agonist or antagonist agents of NPY-Y5 receptor, comprising contacting a NPY-Y5 receptor according to any one of claims 15 to 17 or a cell transformed with and expressing a DNA molecule according to any one of claims 1 to 9, with a test agent under conditions enabling the activation of the NPY-Y5 receptor, and detecting an increase or decrease in the NPY-Y5 receptor activity.

21. A nucleic acid probe comprising a nucleotide sequence of 10 or more nucleotides capable of specifically hybridizing to a unique sequence within the DNA molecule according to any one of claims 1 to 9.

22. An antisense nucleic acid molecule comprising a nucleotide sequence capable of specifically hybridizing to an mRNA molecule which encodes NPY-Y5 receptor so as to prevent translation of the mRNA molecule.

FIGURE 1

Sequence Range: 1 to 8371

```
                                                                      70
        *         *         *         *         *         *         *
CTGCAGCGGCCGGGGCGCCCCGAGGTACGGGCTCCCGCCCCTCCCTGCCAACCCCTTTCGCGCCGGGTAG

                                                                     140
        *         *         *         *         *         *         *
GCCTGCACCGAGGGGCCGTGGCGGGTCCCCGCGCGGGCTGCGAGTCTGCGCAGGTCCCTGGGAGCCCGCA

                                                                     210
        *         *         *         *         *         *         *
CCCGTCTCTGGTGCCAGGGCGTTGTCGGGGGTCCCAAGAGAGCGGGGTGGGGAAGGTGAAGGGAGCGCGG

                                                                     280
        *         *         *         *         *         *         *
CTGGAAAAATGGGGATTAGGGTGGCGGAACAGGCACTTGTCAGGAGTGAAGAGACAGCGGAGAGGGTACT

                                                                     350
        *         *         *         *         *         *         *
GGGCTGAATTCTTTCGTGCCGAGCAGGTCCCTCCGGTTCCCAACTCACCCGGGTGGAGCAGGCGCGGGCC

                                                                     420
        *         *         *         *         *         *         *
GAACCCGGGAGGAGAGTGTCGGGGATCCGCGAAGGAGCCTCCTGGGGATGGGGCGGGGGATGGACAAAGC

                                                                     490
        *         *         *         *         *         *         *
GCTGCCCCCGGCTGGACACGCTCTGGCGCTAGCCCGGCTGGCATCCGGAGCTGGGAACAGCAGCCCGCGG

                                                                     560
        *         *         *         *         *         *         *
GGTGCCCGGGTCAGGGCTCAACCTAGCGGGTCTCTGGCGAGGCCGGGGGCGCAGCCCGCGGGGCGCCACT

                                                                     630
        *         *         *         *         *         *         *
CAGGCCGTCCAGCTGCCGCGCGGTCCAGCGCTGACCCGAGCCCGGGAGGCAGCTGCGCTCTAAGGTTTGC

                                                                     700
        *         *         *         *         *         *         *
GCTCCTGTTTGCGAGGTGTCTTCATATAACAAATGCGAGCAATAACAAACATCCATAGAACTCGAATTCC

                                                                     770
        *         *         *         *         *         *         *
AGAAACGGGAATTCTTTTTTCCAAGTTCACAGACCTTTAGTTAATCTTTTAAAGGAACTGAGGCGTTGTG

                                                                     840
        *         *         *         *         *         *         *
TTGGACCAAAGCCAAAACGATTTTACCTTACACCATGGAAAATAGCCTAAGGCTCTTTTCAGCAGAATTT

                                                                     910
        *         *         *         *         *         *         *
TTGGCAGTCCGAATGCAATTTTTAGATTTCAGATTTCTCAAGGGAAGAGAAACTCTGCTGTTAGAATTTG

                                                                     980
        *         *         *         *         *         *         *
GAAGGGAGGGTGGTGCATGCCTGTGTGTTTGTCAGCTGAGCAGAGCTGTATTTATCTTTCCAATTCAAAT

                                                                    1050
        *         *         *         *         *         *         *
```

FIGURE 1 Cont.

1120
CGATCACAGCAAAACAGACAATAGTTGATATTGTATCATTGCAGGAGGAAAAAGAATTACATATATTTTA

1190
TTCTTTTGTGTGATTGTCATCCTTTGTGAAAAGAATGATGTGTATTTTCATAAAGCAAAAAATTATTCAA

1260
ACAAAGAAACCTTATTTAAATGTACAAGTCAGACTTTTAATATCCTTTGAATTCCCTGCAGTTCCTCCTA

1330
TTATTCTTGAGAACTATCTACTTGGTTAAAATACTTAAATCTATTCAGAAGGTTTCATTTGTCTAGGTGT

1400
CAGATATAGAAGAGTTTATAAGAAAATTCCAGTAAACCTTTAAAAAGATATTATTTTTTATAAGTTGCCA

1470
TAGTTTAATAAAGAACTTTTATTTTTCACACTTTTTACTCAGAGATTAAAGTTCTGTGTTTCAGCCTGGA

1540
AATTCTGATGGTGGGAGATACAACTAATACAAAAGAGAATGAGTAAATATAGTAATTAGGTATGACAAAA

1610
GTCTCATGCTGTCAATATCAGATTTCTTGTCAAATAATATTCCATGTTAAAATATTTTTTCTCTGGCTAT

1680
ATTTCATAATTTATATAGCAATTTCAGAAGATTCACATATATCATTACTTTTATAATAGATAAAATATGT

1750
TGCATAAAAATGACAGCACTCGTAATAACACTTGTTGAAATTTGGATTTCCATTGTAGGTCTGCTCATTG

1820
TGTTTTCAGGAAAAAGGAAGGGAAAGGGTAAGTTTAATGGAAAAAATCCTGCTTTTTTGTTTGTTTTTTC

1890
ATTTAAGTGCGTTCCTGTACCTTGAGTTTTCAAGTTAAATCTTATTGTACAAAATTTTCCTAATGTTTAA

1960
ACTAGGCCCTGGCTACCAGGAGGCACTTTTAAAAAAACTACACGTCCACCACCACCCCTCCCCCACCCGC

2030
CCTCCCTGCCTCCAGCATTTGCAATATTCATTATTTAGTTGTAAGAAGAAATTCTTCCTTCATTGGAGCA

2100
AAGATTCACAGAATGTTCATTCTGTGCAGACTATATATTAGATATTACATGTGTGTATGTTTATGTGGTA

FIGURE 1 Cont.

GATGGTGTGGGGTGGGGCTAGAGGGAGAGCAGGAGAAAGTTGACTACAGTCACACCAAAATAAAATGAAT

2240

AAATGAGTGTTGAATGAATCAAGTGCTAAGAGAGAATTTTTAAATTGCTTACCAATCTATCAGTAGCTAC

2310

ATAAGTATTCATTATATTCAGCAGTAATGCATGTGTCCATGCTATAGAGAAATAATATATTACTATCAGT

2380

CAGGAGAATGCCATTCATTTATTAATTCATTCATCATCCAATTTGGGCCTTTTTTATATCTCAGCAATCTA

2450

CAGTTACTCAGGGTGTAGAGCTTGAATTAATCTATATAGAATATTCTTGGCATAGCACCTTGCATTAGTC

2520

GTCTTTATGCTTAGAGCAGAGCAGAGCACCTAGCAGAATATATGTTCAATAAATACTTTTTGAATGAATA

2590

AAAGAAGGAACAACTAATCATTCTTAGCTGTTCATTAATAGAAGGTGCCTACCCCTTTAAAATTATATAT

2660

AAATTATCTCTTTCTTAAAATACTCAAATGTTTTAAGGAATGAAAGAAGCATCCTCAGTTTTTTCTCCAG

2730

TGTCCAATGAATACTCAAGATGGCATTTATTTCATCTTCTTACTAAGGAGATGTGGTTTTACAATTTAAT

2800

GCATTCAATATTTTATGTGCATATATTTAAAATAAAAGTTTTAATAACAGACTGCACAGTCGCGGAAATG

2870

GATATACTTCTTTTTTCATTTACATTTTTTAAATGTTGTAAATATATCTTACAGTTTTAGTTGCATGTTG

2940

CTTGTGTGATAGCCTTTATCAATGAAGTTATCCAAATTTAAAGTGCTAAACTATCTTTATTGTCTGTCTA

3010

GGTATCTCCTCCTCATTGCATTTTGGGGCCATTTGAAACATCTATAATTTCAATGGTTCTCTATAAATGT

3080

ATATATAAAGATACATATACACACATATATATGTACACACAAAAATATAGTCATACTCTATCCTGAATTT

3150

TCCCACATTGCCAGAATGATTCATTTCTGTTATTTTAAAGCAAGGGAAATTAAACTGCTTTTCTAAAACG

3220

ATTGGTAAGAAATATTTACTTAGCATCCACTATGTGTAATATGCTTTATTAAACATCATTTCTACAATGA

FIGURE 1 Cont.

```
                                                                    3290
         *         *         *         *         *         *         *
AAATAATTAAGAGTTTTATCTCCATTCGAATATAATAGAGAGGTCTAACCACATGGAATGGAGAAAAATC

                                                                    3360
         *         *         *         *         *         *         *
TGAATTTTAGACTCAAAACTACATTGTTTCTATTACCACAAATTGTGCTGCATCTTCTCTTTCTTCAAAA

                                                                    3430
         *         *         *         *         *         *         *
AATTTTGGACAGCAATTTTACACTAAGTAAGTATCATCCACAGTTACATGTTCCAAAAAGGCACAAAGCC

                                                                    3500
         *         *         *         *         *         *         *
GTTGTAGAAGGGGCCATCTAATTTCTCTCTTGTTCTTGCTTAGGTGTTACAAGGAAAGGCTATCGGTAAC

                                                                    3570
         *         *         *         *         *         *         *
AACTGACCTGCCACAAAGTTAGAAGAAAGGATTGATTCAAGAAAGTAAGTCAAGAGAAGAACAACTAAGC

                                                                    3640
         *         *         *         *         *         *         *
AGGATTGCAGTTACAAGCAGCCTGTACACAATTATAAATATAAATAGGATCATGAATAAGCTGAATTGAG

                                                                    3710
         *         *         *         *         *         *         *
CCAGGGGATCATCAGAACTCAGGAAATTAGGCAAAAGCACCAGTCAAAGCTGTTTTGATTAGAAGCTTGC

                                                                    3780
         *         *         *         *         *         *         *
TGACCTATCCAGAGTAGGTGCTGAGAGGCCATTGACTGGGAATATGATGAATAATATGATTCAGTAGGTC

                                                                    3850
         *         *         *         *         *         *         *
ATGCGAGTCACTTTTGTACCAGGTGTTCTTTGTCATTGAGGCAATATCAATGTAAATTGTTGGCTAGGGT

                                                                    3920
         *         *         *         *         *         *         *
CTAAGAATGAATGAATACAATCCTAAGTCTTTGAATTAACTTATCCTTTAAAAGGATGTAGTTAGCTTCC

                                                                    3990
         *         *         *         *         *         *         *
AGAAAATAATTTGGTCAACATAGAATCACTTGTAGAAGTTGTGAAAAACTTGTAACTTTTCTCATAGCAC

                                                                    4060
         *         *         *         *         *         *         *
AATGATGACTCTGTCATCCTGTTTGAAACTTGCTACACATAGAACTGAAGTTAAACTTATTTGTAATGAA

                                                                    4130
         *         *         *         *         *         *         *
TGTATGTACACAATAGTATTTGCCATTTGGAAATTTATTGAACGAAGACCTGCAGGTCCCTCATAAATTA

                                                                    4200
         *         *         *         *         *         *         *
AAGATAACAGTGTTTACTATTAATTTAAATAAACATGTATTTTTATAGTTTTAGTATAATTATTCAATTA

                                                                    4270
         *         *         *         *         *         *         *
TAGATCTAGAAATAAGTAGATAAACATATATTGATAGGTAACAAAAGTGGTTTTTTAACTATATATATCA
```

FIGURE 1 Cont.

CAATCTCTACGACAATGTATTTATTGGAATTAATTTCTTTGTTGGTTTGTGTTTTCTGTAGGAAATTCTT

4410

GTTAAAAAAACATTAAAGTGGCTGGGCACAGTGGTTCATGCCTCTCATGCCTATAATCCCAACAGTTTGG

4480

GAGGCCAAGGTGGGAGGTTTACTTGAGGCCAGGAGTTTGAGACCAGCCTGGGCAACATAGCCAGACCCCA

4550

TCTCCACAAAAAATAGAAAGATTAGCCAGATGTAGTGGCACGTGCCTGTAGTCCACGTGCCTGTAGTCCA

4620

GCTGCTTGGGAGGCTGAGATGAGAGGATTGCTTGAGTCCAGGCGTTCAAGGTTACAATGAGCTGTGGTCA

4690

CACTACTGCACCCCAGCCTGGGCAACAGAATGAGACCCTTTTTCTAAGAAAAATAAAAAGGTAAAAAAAA

4760

AAAAAAGTCCTTTTTTTTTTAAACGAGAGGAGGGAGTCCTTTTGCCTCTTATTGGTATGTTATAGGCAAT

4830

TTAGTGCTTCATCAGGCAGTAGCATCAAAAGTCTAATATGTAGAGGTAAATACGTAATGCCATTGATGTA

4900

TGACATTAATTTAATTTGAAATGAAGAAAACTTATTACCGGGAGTTATATTAATATCACTGCTACATTTA

4970

CGTTTAAGGTATAATGTTTTCCTTGAACAATGAATTCATTGAGTCGTTCATAAGCCAAAATCTATACACA

5040

GTTTTTAAATTAATCAACAGGTGAAATTTGATTGTTTGTTTTTTTAAAACGCCAACAGCCTGCTAGTCTG

5110

TCAGTGGTTGTCCTAATCAGAGATAATCTGGCACATCTCAAACCATTGAGGATTGGTCACAGAAAGATGT

5180

CATCATCCAGCATTGCGTCCACACAGTCAACAGTAGAGTTTGATAAATATATTTAATGAGTGCCTACTAT

5250

ATGCATCTGGGTCATGAGATAGTGATCCTATTCTCAAGGAGCATAAATTTGAACATTGTACGAACTAGGT

5320

GATATTTGTTACTAGAGTTTTGTTTGAACGTTTTATTCTCTCATAAACATTTATTTAATACCTGCAGTGA

5390

FIGURE 1 Cont.

```
                                                                    5460
          *         *         *         *         *         *         *
TTGTAAATAAACAAGGTAGATGGGTAGGCATTATAATGCAATGAAAGCAGATTATGATATGTAGCATCAG

                                                                    5530
          *         *         *         *         *         *         *
ACAACTGTAAACAGAATGTAACAGGAGTTCTGAAGAGGAGATCATGTCCAGCCGAGTTGACCAGGACAAG

                                                                    5600
          *         *         *         *         *         *         *
TGACTTTTAAGTTTGGCCTAGATTGAGATAGAAATAAATGGAATTTTTATGATAAGATTATGTGACTATA

                                                                    5670
          *         *         *         *         *         *         *
CTACATACCAGGTATATTGACTTGGAGAATAATATTAATGAGTGATTGCAAAGCATGTATCTTGAAGTTC

                                                                    5740
          *         *         *         *         *         *         *
TTGTCTACATTTGCCTTTTTCTTTCCTTACGTTATTTACTACAGAAATTTTAAAAATGCAATCTACTACC

                                                                    5810
          *         *         *         *         *         *         *
TTAACATAAATTAATACATCTTAGAAGTAATGATAAAATTAAATTTACTATAATCATTATTGGCTGATAC

                                                                    5880
          *         *         *         *         *         *         *
TTGAATTGCCCTTGGAACGAGTTAAAGGTATCATAAACTTTCTGGGCTGGGCACGGTGCTCACGCCTGTA

                                                                    5950
          *         *         *         *         *         *         *
ATCCCAGCACTTTGGGAGGCCGAGGCGGGCGGATCACGAGGTCAGGAGATCGAGACCACGGTGAAACCCG

                                                                    6020
          *         *         *         *         *         *         *
GTCTCTACTAAAAATACAAAAAATTAGCTGGGCGCAGTGGCGGGCGCCTGTAGTCCCAGCTACTCGGGAG

                                                                    6090
          *         *         *         *         *         *         *
GCTGAGGCAGGAGAATGGCGTGAACCCGGGAGGCGGAGCTTGCAGTGAGCCGAGATGGCGCCACAGCACT

                                                                    6160
          *         *         *         *         *         *         *
CCAGCCTGGGCGACAGAGCGAGACTCCGTCTCAAAAAAAAAAAAAAAAAAAAAGATATCATAAACTTCCTT

                                                                    6230
          *         *         *         *         *         *         *
AGGAGATTAATAAGGTCACGGGAGCTGATTGTAATATTTAGTTTCCCTCTGAATAGATTAATTTAAAGTA

                                                                    6300
          *         *         *         *         *         *         *
GTCATGTAATGTTTTTTTGGTTGCTTACAAATGTCTTTTTATTCCAAGCAGGACTATAATATGGATTTAG
                                                              M   D   L>

                                                                    6370
          *         *         *         *         *         *         *
AGCTCGACGAGTATTATAACAAGACACTTGCCACAGAGAATAATACTGCTGCCACTCGGAATTCTGATTT
E   L   D   E   Y   Y   N   K   T   L   A   T   E   N   N   T   A   A   T   R   N   S   D   F>

                                                                    6440
          *         *         *         *         *         *         *
CCCAGTCTGGGATGACTATAAAAGCAGTGTAGATGACTTACAGTATTTTCTGATTGGGCTCTATACATTT
                                                                  Y   T   F>
```

FIGURE 1 Cont.

```
                                                                    6510
          *         *         *         *         *         *         *
GTAAGTCTTCTTGGCTTTATGGGGAATCTACTTATTTTAATGGCTCTCATGAAAAAGCGTAATCAGAAGA
 V  S  L  L  G  F  M  G  N  L  L  I  L  M  A  L  M  K  K  R  N  Q  K>

                                                                    6580
          *         *         *         *         *         *         *
CTACGGTAAACTTCCTCATAGGCAATCTGGCCTTTTCTGATATCTTGGTTGTGCTGTTTTGCTCACCTTT
T  T  V  N  F  L  I  G  N  L  A  F  S  D  I  L  V  V  L  F  C  S  P  F>

                                                                    6650
          *         *         *         *         *         *         *
CACACTGACGTCTGTCTTGCTGGATCAGTGGATGTTTGGCAAAGTCATGTGCCATATTATGCCTTTTCTT
  T  L  T  S  V  L  L  D  Q  W  M  F  G  K  V  M  C  H  I  M  P  F  L>

                                                                    6720
          *         *         *         *         *         *         *
CAATGTGTGTCAGTTTTGGTTTCAACTTTAATTTTAATATCAATTGCCATTGTCAGGTATCATATGATAA
 Q  C  V  S  V  L  V  S  T  L  I  L  I  S  I  A  I  V  R  Y  H  M  I>

                                                                    6790
          *         *         *         *         *         *         *
AACATCCCATATCTAATAATTTAACAGCAAACCATGGCTACTTTCTGATAGCTACTGTCTGGACACTAGG
K  H  P  I  S  N  N  L  T  A  N  H  G  Y  F  L  I  A  T  V  W  T  L  G>

                                                                    6860
          *         *         *         *         *         *         *
TTTTGCCATCTGTTCTCCCCTTCCAGTGTTTCACAGTCTTGTGGAACTTCAAGAAACATTTGGTTCAGCA
  F  A  I  C  S  P  L  P  V  F  H  S  L  V  E  L  Q  E  T  F  G  S  A>

                                                                    6930
          *         *         *         *         *         *         *
TTGCTGAGCAGCAGGTATTTATGTGTTGAGTCATGGCCATCTGATTCATACAGAATTGCCTTTACTATCT
 L  L  S  S  R  Y  L  C  V  E  S  W  P  S  D  S  Y  R  I  A  F  T  I>

                                                                    7000
          *         *         *         *         *         *         *
CTTTATTGCTAGTTCAGTATATTCTGCCCTTAGTTTGTCTTACTGTAAGTCATACAAGTGTCTGCAGAAG
S  L  L  L  V  Q  Y  I  L  P  L  V  C  L  T  V  S  H  T  S  V  C  R  S>

                                                                    7070
          *         *         *         *         *         *         *
TATAAGCTGTGGATTGTCCAACAAAGAAAACAGACTTGAAGAAAATGAGATGATCAACTTAACTCTTCAT
  I  S  C  G  L  S  N  K  E  N  R  L  E  E  N  E  M  I  N  L  T  L  H>

                                                                    7140
          *         *         *         *         *         *         *
CCATCCAAAAAGAGTGGGCCTCAGGTGAAACTCTCTGGCAGCCATAAATGGAGTTATTCATTCATCAAAA
 P  S  K  K  S  G  P  Q  V  K  L  S  G  S  H  K  W  S  Y  S  F  I  K>

                                                                    7210
          *         *         *         *         *         *         *
AACACAGAAGAAGATATAGCAAGAAGACAGCATGTGTGTTACCTGCTCCAGAAAGACCTTCTCAAGAGAA
K  H  R  R  R  Y  S  K  K  T  A  C  V  L  P  A  P  E  R  P  S  Q  E  N>

                                                                    7280
          *         *         *         *         *         *         *
CCACTCCAGAATACTTCCAGAAAACTTTGGCTCTGTAAGAAGTCAGCTCTCTTCATCCAGTAAGTTCATA
  H  S  R  I  L  P  E  N  F  G  S  V  R  S  Q  L  S  S  S  S  K  F  I>
```

FIGURE 1 Cont.

```
CCAGGGGTCCCCACTTGCTTTGAGATAAAACCTGAAGAAAATTCAGATGTTCATGAATTGAGAGTAAAAC
 P  G  V  P  T  C  F  E  I  K  P  E  E  N  S  D  V  H  E  L  R  V  K>

                                                                    7420
GTTCTGTTACAAGAATAAAAAAGAGATCTCGAAGTGTTTTCTACAGACTGACCATACTGATATTAGTATT
R  S  V  T  R  I  K  K  R  S  R  S  V  F  Y  R  L  T  I  L  I  L  V  F>

                                                                    7490
TGCTGTTAGTTGGATGCCACTACACCTTTTCCATGTGGTAACTGATTTTAATGACAATCTTATTTCAAAT
  A  V  S  W  M  P  L  H  L  F  H  V  V  T  D  F  N  D  N  L  I  S  N>

                                                                    7560
AGGCATTTCAAGTTGGTGTATTGCATTTGTCATTTGTTGGGCATGATGTCCTGTTGTCTTAATCCAATTC
 R  H  F  K  L  V  Y  C  I  C  H  L  L  G  M  M  S  C  C  L  N  P  I>

                                                                    7630
TATATGGGTTTCTTAATAATGGGATTAAAGCTGATTTAGTGTCCCTTATACACTGTCTTCATATGTAATA
L  Y  G  F  L  N  N  G  I  K  A  D  L  V  S  L  I  H  C  L  H  M>

                                                                    7700
ATTCTCACTGTTTACCAAGGAAAGAACAAATGCTGGGGTCATATAAAATATATTTATGATAACTATTTAC

                                                                    7770
ATATAATAAATAGAAATTTTGTTAACATGGAATTTAATTTATGTGAAAGAGTTCTGGATTCAAATGTCAG

                                                                    7840
TTCATAATATATGGAAGATAATTTTATGTGTTATAGTAGGATTAATTTATTTAGTTGTGCAGTCAGTGTC

                                                                    7910
AATCCAATCTGTAATTTCACTTTAGAAGGTTGTATTACCTTCCACTTCCATGTTGTCTTATAAACAAATG

                                                                    7980
AATTGTATTTTTTGTTGAAAGTAAAAGTTATATCTAACCAACTCAGTACTTTTGTCCAAAAATATAATAA

                                                                    8050
GAAAAAATTTTTCTCGAGGAACTTTTAATTTCAAACTTGAAGAATATCTACCAGCTATCTATATCATTTC

                                                                    8120
TACTCCATAGGCTTCTTAATGTTTAGTTTGTGAAGTACAGAAAAAATTTAATATGCCTGGAAAATCACAA

                                                                    8190
CTAAATGACAGATGTATGCCCAAATTATGATTATAATCTTCAACATTAACTACAGTTTTGGAAGTCCTGT

                                                                    8260
AGGAAAATGCTATTGCCTATTGAGAATTGGTCAAATTGTCAATTTAACTCCACTGTCCTAGTAATACACA
```

FIGURE 1 Cont.

AGTAATTTACCAAATAAAGAATTTTAAATCCTTTCCAGACTCATTATACAACATTAAACACTACCAATAA

* * * *

AAGTTGTTTTCATATACATCAAAACTATTCTAAAATGTGAA

FIGURE 2

Sequence Range: 1 to 2143

```
                                                                    70
        *         *         *         *         *         *         *
AGCTCGTCGACCTGACCTGCCACAAAGTTAGAAGAAAGGATTGATTCAAGAAAGACTATAATATGGATTT
                                                          M   D   L>

                                                                   140
        *         *         *         *         *         *         *
AGAGCTCGACGAGTATTATAACAAGACACTTGCCACAGAGAATAATACTGCTGCCACTCGGAATTCTGAT
  E   L   D   E   Y   Y   N   K   T   L   A   T   E   N   N   T   A   A   T   R   N   S   D>

                                                                   210
        *         *         *         *         *         *         *
TTCCCAGTCTGGGATGACTATAAAAGCAGTGTAGATGACTTACAGTATTTTCTGATTGGGCTCTATACAT
 F   P   V   W   D   D   Y   K   S   S   V   D   D   L   Q   Y   F   L   I   G   L   Y   T>

                                                                   280
        *         *         *         *         *         *         *
TTGTAAGTCTTCTTGGCTTTATGGGGAATCTACTTATTTTAATGGCTCTCATGAAAAAGCGTAATCAGAA
F   V   S   L   L   G   F   M   G   N   L   L   I   L   M   A   L   M   K   K   R   N   Q   K>

                                                                   350
        *         *         *         *         *         *         *
GACTACGGTAAACTTCCTCATAGGCAATCTGGCCTTTTCTGATATCTTGGTTGTGCTGTTTTGCTCACCT
  T   T   V   N   F   L   I   G   N   L   A   F   S   D   I   L   V   V   L   F   C   S   P>

                                                                   420
        *         *         *         *         *         *         *
TTCACACTGACGTCTGTCTTGCTGGATCAGTGGATGTTTGGCAAAGTCATGTGCCATATTATGCCTTTTC
 F   T   L   T   S   V   L   L   D   Q   W   M   F   G   K   V   M   C   H   I   M   P   F>

                                                                   490
        *         *         *         *         *         *         *
TTCAATGTGTGTCAGTTTTGGTTTCAACTTTAATTTTAATATCAATTGCCATTGTCAGGTATCATATGAT
L   Q   C   V   S   V   L   V   S   T   L   I   L   I   S   I   A   I   V   R   Y   H   M   I>

                                                                   560
        *         *         *         *         *         *         *
AAAACATCCCATATCTAATAATTTAACAGCAAACCATGGCTACTTTCTGATAGCTACTGTCTGGACACTA
  K   H   P   I   S   N   N   L   T   A   N   H   G   Y   F   L   I   A   T   V   W   T   L>

                                                                   630
        *         *         *         *         *         *         *
GGTTTTGCCATCTGTTCTCCCCTTCCAGTGTTTCACAGTCTTGTGGAACTTCAAGAAACATTTGGTTCAG
 G   F   A   I   C   S   P   L   P   V   F   H   S   L   V   E   L   Q   E   T   F   G   S>

                                                                   700
        *         *         *         *         *         *         *
CATTGCTGAGCAGCAGGTATTTATGTGTTGAGTCATGGCCATCTGATTCATACAGAATTGCCTTTACTAT
A   L   L   S   S   R   Y   L   C   V   E   S   W   P   S   D   S   Y   R   I   A   F   T   I>

                                                                   770
        *         *         *         *         *         *         *
CTCTTTATTGCTAGTTCAGTATATTCTGCCCTTAGTTTGTCTTACTGTAAGTCATACAAGTGTCTGCAGA
  S   L   L   L   V   Q   Y   I   L   P   L   V   C   L   T   V   S   H   T   S   V   C   R>

                                                                   840
        *         *         *         *         *         *         *
AGTATAAGCTGTGGATTGTCCAACAAAGAAAACAGACTTGAAGAAAATGAGATGATCAACTTAACTCTTC
 S   I   S   C   G   L   S   N   K   E   N   R   L   E   E   N   E   M   I   N   L   T   L>
```

FIGURE 2 Cont.

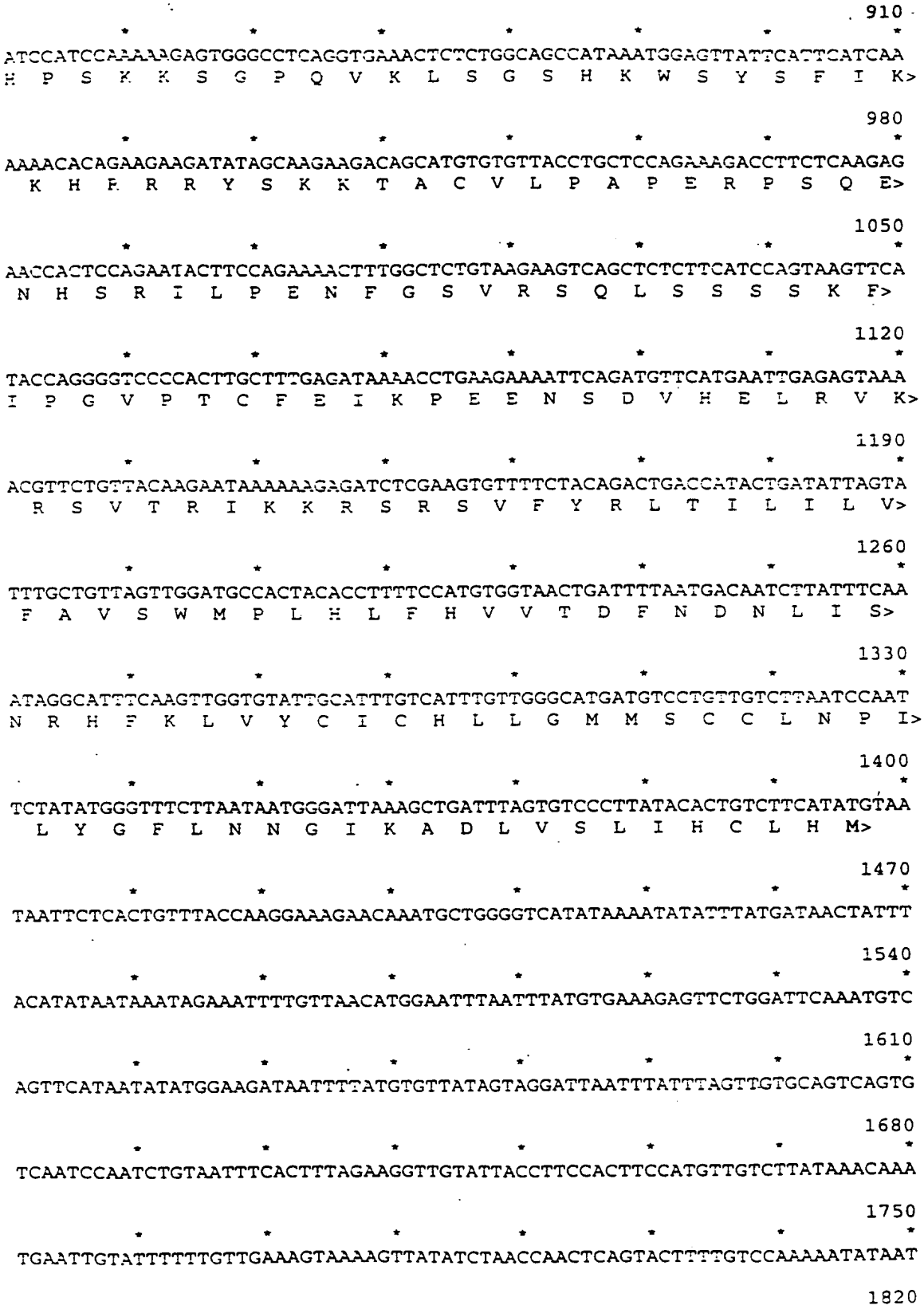


FIGURE 2 Cont.

AAGAAAAAATTTTTCTCGAGGAACTTTTAATTTCAAACTTGAAGAATATCTACCAGCTATCTATATCATT

1890

TCTACTCCATAGGCTTCTTAATGTTTAGTTTGTGAAGTACAGAAAAAATTTAATATGCCTGGAAAATCAC

1960

AACTAAATGACAGATGTATGCCCAAATTATGATTATAATCTTCAACATTAACTACAGTTTTGGAAGTCCT

2030

GTAGGAAAATGCTATTGCCTATTGAGAATTGGTCAAATTGTCAATTTAACTCCACTGTCCTAGTAATACA

2100

CAAGTAATTTACCAAATAAAGAATTTTAAATCCTTTCCAGACTCATTATACAACATTAAACACTACCAAT

AAAAGTTGTTTTCATATACATCAAAACTATTCTAAAATGTGAA

FIGURE 3

Sequence Range: 1 to 2286

```
                                                                      70
        *         *         *         *         *         *         *
GAATTCGGCACGAGGGGTTTGCAAGGTGGCTTGGAAGTCAACTGCCAGTAGGAAATAGCCATCCACACAC

                                                                     140
        *         *         *         *         *         *         *
CTGAGTTCCAAGGGGGAAGAAAGAGATTCTTATCTGATTCTAGTATGGAGTTTAAGCTTGAGGAGCATTT
                                              M  E  F  K  L  E  E  H  F>

                                                                     210
        *         *         *         *         *         *         *
TAACAAGACATTTGTCACAGAGAACAATACAGCTGCTGCTCGGAATGCAGCCTTCCCTGCCTGGGAGGAC
  N  K  T  F  V  T  E  N  N  T  A  A  A  R  N  A  A  F  P  A  W  E  D>

                                                                     280
        *         *         *         *         *         *         *
TACAGAGGCAGCGTAGACGATTTACAATACTTTCTGATTGGGCTCTATACATTCGTAAGTCTTCTTGGCT
 Y  R  G  S  V  D  D  L  Q  Y  F  L  I  G  L  Y  T  F  V  S  L  L  G>

                                                                     350
        *         *         *         *         *         *         *
TTATGGGCAATCTACTTATTTTAATGGCTGTTATGAAAAAGCGCAATCAGAAGACTACAGTGAACTTTCT
F  M  G  N  L  L  I  L  M  A  V  M  K  K  R  N  Q  K  T  T  V  N  F  L>

                                                                     420
        *         *         *         *         *         *         *
CATAGGCAACCTGGCCTTCTCCGACATCTTGGTCGTCCTGTTTTGCTCCCCTTTCACCCTGACCTCTGTC
  I  G  N  L  A  F  S  D  I  L  V  V  L  F  C  S  P  F  T  L  T  S  V>

                                                                     490
        *         *         *         *         *         *         *
TTGTTGGATCAGTGGATGTTTGGCAAAAGCATGTGCCATATCATGCCGTTCCTTCAATGTGTGTCAGTTC
 L  L  D  Q  W  M  F  G  K  S  M  C  H  I  M  P  F  L  Q  C  V  S  V>

                                                                     560
        *         *         *         *         *         *         *
TGGTTTCAACTCTGATTTTAATATCAATTGCCATTGTCAGGTATCATATGATAAAGCACCCTATTTCTAA
L  V  S  T  L  I  L  I  S  I  A  I  V  R  Y  H  M  I  K  H  P  I  S  N>

                                                                     630
        *         *         *         *         *         *         *
CAATTTAACGGCAAACCATGGCTACTTCCTGATAGCTACTGTCTGGACACTGGGCTTTGCCATCTGTTCT
  N  L  T  A  N  H  G  Y  F  L  I  A  T  V  W  T  L  G  F  A  I  C  S>

                                                                     700
        *         *         *         *         *         *         *
CCCCTCCCAGTGTTTCACAGTCTTGTGGAACTTAAGGAGACCTTTGGCTCAGCACTGCTGAGTAGCAAAT
 P  L  P  V  F  H  S  L  V  E  L  K  E  T  F  G  S  A  L  L  S  S  K>

                                                                     770
        *         *         *         *         *         *         *
ATCTCTGTGTTGAGTCATGGCCCTCTGATTCATACAGAATTGCTTTCACAATCTCTTTATTGCTAGTGCA
Y  L  C  V  E  S  W  P  S  D  S  Y  R  I  A  F  T  I  S  L  L  L  V  Q>

                                                                     840
        *         *         *         *         *         *         *
GTATATCCTGCCTCTAGTATGTTTAACGGTAAGTCATACCAGCGTCTGCCGAAGCATAAGCTGTGGATTG
  Y  I  L  P  L  V  C  L  T  V  S  H  T  S  V  C  R  S  I  S  C  G  L>
```

FIGURE 3 Cont.

```
TCCCACAAAGAAAACAGACTCGAAGAAAATGAGATGATCAACTTAACCCTACAGCCATCCAAAAAGAGCA
 S  H  K  E  N  R  L  E  E  N  E  M  I  N  L  T  L  Q  P  S  K  K  S>

                                                                     980
GGAACCAGGCAAAAACCCCCAGCACTCAAAAGTGGAGCTACTCATTCATCAGAAAGCACAGAAGGAGGTA
P  N  Q  A  K  T  P  S  T  Q  K  W  S  Y  S  F  I  R  K  H  R  R  R  Y>

                                                                    1050
CAGCAAGAAGACGGCCTGTGTCTTACCCGCCCCAGCAGGACCTTCCCAGGGGAAGCACCTAGCCGTTCCA
  S  K  K  T  A  C  V  L  P  A  P  A  G  P  S  Q  G  K  H  L  A  V  P>

                                                                    1120
GAAAATCCAGCCTCCGTCCGTAGCCAGCTGTCGCCATCCAGTAAGGTCATTCCAGGGGTCCCAATCTGCT
 E  N  P  A  S  V  R  S  Q  L  S  P  S  S  K  V  I  P  G  V  P  I  C>

                                                                    1190
TTGAGGTGAAACCTGAAGAAAGCTCAGATGCTCATGAGATGAGAGTCAAGCGTTCCATCACTAGAATAAA
F  E  V  K  P  E  E  S  S  D  A  H  E  M  R  V  K  R  S  I  T  R  I  K>

                                                                    1260
AAAGAGATCTCGAAGTGTTTTCTACAGACTGACCATACTGATACTCGTGTTCGCCGTTAGCTGGATGCCA
  K  R  S  R  S  V  F  Y  R  L  T  I  L  I  L  V  F  A  V  S  W  M  P>

                                                                    1330
CTCCACGTCTTCCACGTGGTGACTGACTTCAATGATAACTTGATTTCCAATAGGCATTTCAAGCTGGTAT
 L  H  V  F  H  V  V  T  D  F  N  D  N  L  I  S  N  R  H  F  K  L  V>

                                                                    1400
ACTGCATCTGTCACTTGTTAGGCATGATGTCCTGTTGTCTAAATCCGATCCTATATGGTTTCCTTAATAA
Y  C  I  C  H  L  L  G  M  M  S  C  C  L  N  P  I  L  Y  G  F  L  N  N>

                                                                    1470
TGGTATCAAAGCAGACTTGAGAGCCCTTATCCACTGCCTACACATGTCATGATTCTCTCTGTGCACCAAA
  G  I  K  A  D  L  R  A  L  I  H  C  L  H  M  S>

                                                                    1540
GAGAGAAGAAACGTGGTAATTGACACATAATTTATACAGAAGTATTCTGGATCTGAATGCCAGTTCGTAA

                                                                    1610
TCTACGTAAGATCATCTTCATGTTATAATATGGTTAATTCAATCAGTTGTGCAGAGTCAATGTCCATCTA

                                                                    1680
ATACAATTTCATGTGTTGAAGTAGTTTACATTATTTTCCATTTTATGTCATTGGTAATAAGTTGAGTGAT

                                                                    1750
ACTCTGTGGTTTAGTGTAAAATGTATGAAGTGACAAGTTGTCCCAAAGAGCATTTAACTACAGATTTAAG
```

FIGURE 3 Cont.

GAATTTCTATTATCTGGGTATCTTCATTTCTATTTCACAGGCTTCTTAACATTTTTTTGTAAAAGTACAA

1890

AAATATTCAAAAGTCAGAACTCTATTACAGATGTATGCATAAAAGATGATTATAATTTTGTAGGAGAAAG

1960

ATCTGCTCCTATTAGTGAAGATTGGTAAAATTGTCAGTTTAACCCGTCTGTCCTACTACTAATATTTAAT

2030

TTTTCAAATATGAAAAGGTTTCAGATTTTGTTTAGATTTATATCACATTAAACACTGTCAAATAAAGGCT

2100

GTTTTTATATGCATCGTTGATGTTCCAAAATGTGAAGTCTAAATGGTGTCTGTATTTCCAATTATTAAAT

2170

AACTTCTAAGATCATTTTTAAAAGTCTGTAGATGGTATGGATAGCTAGTTGTTTGTTAATATAAAGTAAA

2240

AGTAGATAGCTGATTTATGTTGTACCTATGTCGTATGTATATTAGGAGCAGTTTCAGCCCCACAGAACAC

TCTATCGTGTTGTCTCACTAAAGTGAAAGCAAACGAAAAAAAAAAA

FIGURE 4

Sequence Range: 1 to 1585

```
                                                                      70
        *         *         *         *         *         *         *
GTTATTGTCATAGCGTGCTATTGTTCTTCAAGCTGCTAATGGTCACTGTCTTCTTCCAAGCAGGACTCTA

                                                                     140
        *         *         *         *         *         *         *
GTATGGAGGTTAAACTTGAAGAGCATTTTAACAAGACATTTGTCACGGAGAACAATACTGCTGCCAGTCA
  M  E  V  K  L  E  E  H  F  N  K  T  F  V  T  E  N  N  T  A  A  S  Q>

                                                                     210
        *         *         *         *         *         *         *
GAACACGGCCTCCCCTGCCTGGGAGGACTACAGAGGCACAGAGAACAATACTTCTGCTGCTCGGAACACT
  N  T  A  S  P  A  W  E  D  Y  R  G  T  E  N  N  T  S  A  A  R  N  T>

                                                                     280
        *         *         *         *         *         *         *
CCGTTTCCAGTCTGGGAGGACTATAGAGGCAGCGTAGACGACTTACAATACTTCCTGATTGGGCTCTATA
  P  F  P  V  W  E  D  Y  R  G  S  V  D  D  L  Q  Y  F  L  I  G  L  Y>

                                                                     350
        *         *         *         *         *         *         *
CATTTGTAAGTCTTCTTGGTTTTATGGGAAATCTACTTATCTTAATGGCTGTTATGAAAAAGCGCAATCA
T  F  V  S  L  L  G  F  M  G  N  L  L  I  L  M  A  V  M  K  K  R  N  Q>

                                                                     420
        *         *         *         *         *         *         *
GAAGACTACAGTGAACTTTCTCATAGGCAACCTGGCCTTCTCCGACATTTTGGTTGTCCTGTTTTGCTCC
  K  T  T  V  N  F  L  I  G  N  L  A  F  S  D  I  L  V  V  L  F  C  S>

                                                                     490
        *         *         *         *         *         *         *
CCTTTCACCCTGACCTCTGTCTTGTTGGATCAGTGGATGTTCGGCAAAGCCATGTGCCATATCATGCCAT
  P  F  T  L  T  S  V  L  L  D  Q  W  M  F  G  K  A  M  C  H  I  M  P>

                                                                     560
        *         *         *         *         *         *         *
TCCTTCAGTGTGTATCAGTTCTGGTTTCAACTCTGATTTTAATATCGATTGCCATTGTCAGGTATCATAT
F  L  Q  C  V  S  V  L  V  S  T  L  I  L  I  S  I  A  I  V  R  Y  H  M>

                                                                     630
        *         *         *         *         *         *         *
GATAAAGCACCCTATATCTAACAATTTAACAGCAAACCATGGCTACTTCCTGATAGCATCTGTCTGGACA
  I  K  H  P  I  S  N  N  L  T  A  N  H  G  Y  F  L  I  A  S  V  W  T>

                                                                     700
        *         *         *         *         *         *         *
CTGGGCTTTGCCATCTGTTCTCCCCTCCCAGTGTTTCACAGCCTTGTGGAACTTAAGGAAACCTTTGGCT
  L  G  F  A  I  C  S  P  L  P  V  F  H  S  L  V  E  L  K  E  T  F  G>

                                                                     770
        *         *         *         *         *         *         *
CAGCATTGCTAAGCAGCAAGTATTTGTGTGTTGAGTCATGGCCCTCTGATTCATACAGAATTGCTTTCAC
S  A  L  L  S  S  K  Y  L  C  V  E  S  W  P  S  D  S  Y  R  I  A  F  T>

                                                                     840
        *         *         *         *         *         *         *
AATCTCTTTATTGTTAGTTCAGTATATCCTGCCTCTAGTATGTTTAACAGTAAGTCATACTAGTGTCTGC
  I  S  L  L  L  V  Q  Y  I  L  P  L  V  C  L  T  V  S  H  T  S  V  C>
```

FIGURE 4 Cont.

```
AGGAGTATAAGCTGTGGATTGTCCCACAAAGAAAACAGACTCGAAGAAAATGAGATGATCAACTTAACTC
 R  S  I  S  C  G  L  S  H  K  E  N  R  L  E  E  N  E  M  I  N  L  T>

                                                                    980
TACATCCATCCAAAAAGAGTCGGGACCAGGCAAAACTCCCCAGCACTCAAAAGTGGAGCTACTCATTCAT
L  H  P  S  K  K  S  R  D  Q  A  K  L  P  S  T  Q  K  W  S  Y  S  F  I>

                                                                   1050
CAGAAAGCACCGAAGAAGGTACAGCAAGAAGACGGCATGCGTGTTACCCGCCCCAGCAGGACCTTCCCAG
  R  K  H  R  R  R  Y  S  K  K  T  A  C  V  L  P  A  P  A  G  P  S  Q>

                                                                   1120
GAGAAGCACCTAACCGTTCCAGAAAACCCAGGCTCGGTCCGTAGCCAGCTGTCACCATCCAGTAAGGTTA
 E  K  H  L  T  V  P  E  N  P  G  S  V  R  S  Q  L  S  P  S  S  K  V>

                                                                   1190
TTCCAGGGGTCCCGATCTGCTTTGAGGTGAAACCTGAAGAAAGCTCAGATGCTCAGGAGATGAGAGTCAA
I  P  G  V  P  I  C  F  E  V  K  P  E  E  S  S  D  A  Q  E  M  R  V  K>

                                                                   1260
GCGTTCCCTCACGAGAATAAAGAAGAGATCTCGCAGTGTTTTCTACAGACTGACTATATTGATATTAGTG
  R  S  L  T  R  I  K  K  R  S  R  S  V  F  Y  R  L  T  I  L  I  L  V>

                                                                   1330
TTCGCTGTTAGCTGGATGCCACTCCACGTCTTCCACGTGGTGACCGATTTCAATGATAACCTGATTTCCA
 F  A  V  S  W  M  P  L  H  V  F  H  V  V  T  D  F  N  D  N  L  I  S>

                                                                   1400
ATAGGCATTTCAAGCTGGTGTACTGCATCTGTCACTTGTTAGGCATGATGTCCTGTTGTCTTAATCCGAT
N  R  H  F  K  L  V  Y  C  I  C  H  L  L  G  M  M  S  C  C  L  N  P  I>

                                                                   1470
CTTATATGGATTCCTTAATAATGGTATCAAAGCAGACTTGAGAGCCCTTATCCACTGCCTACACATGTCA
  L  Y  G  F  L  N  N  G  I  K  A  D  L  R  A  L  I  H  C  L  H  M  S>

                                                                   1540
TGATTCTCTCTGTGCACCGAGGAGAGAAGAAATGTGGAGACTGCCCACAATACATCTGTGCTAATTGATG

CATAATTTACATAAACGTGTCTGGATCTGAATGCCAGTTTGTAAT
```

FIGURE 5

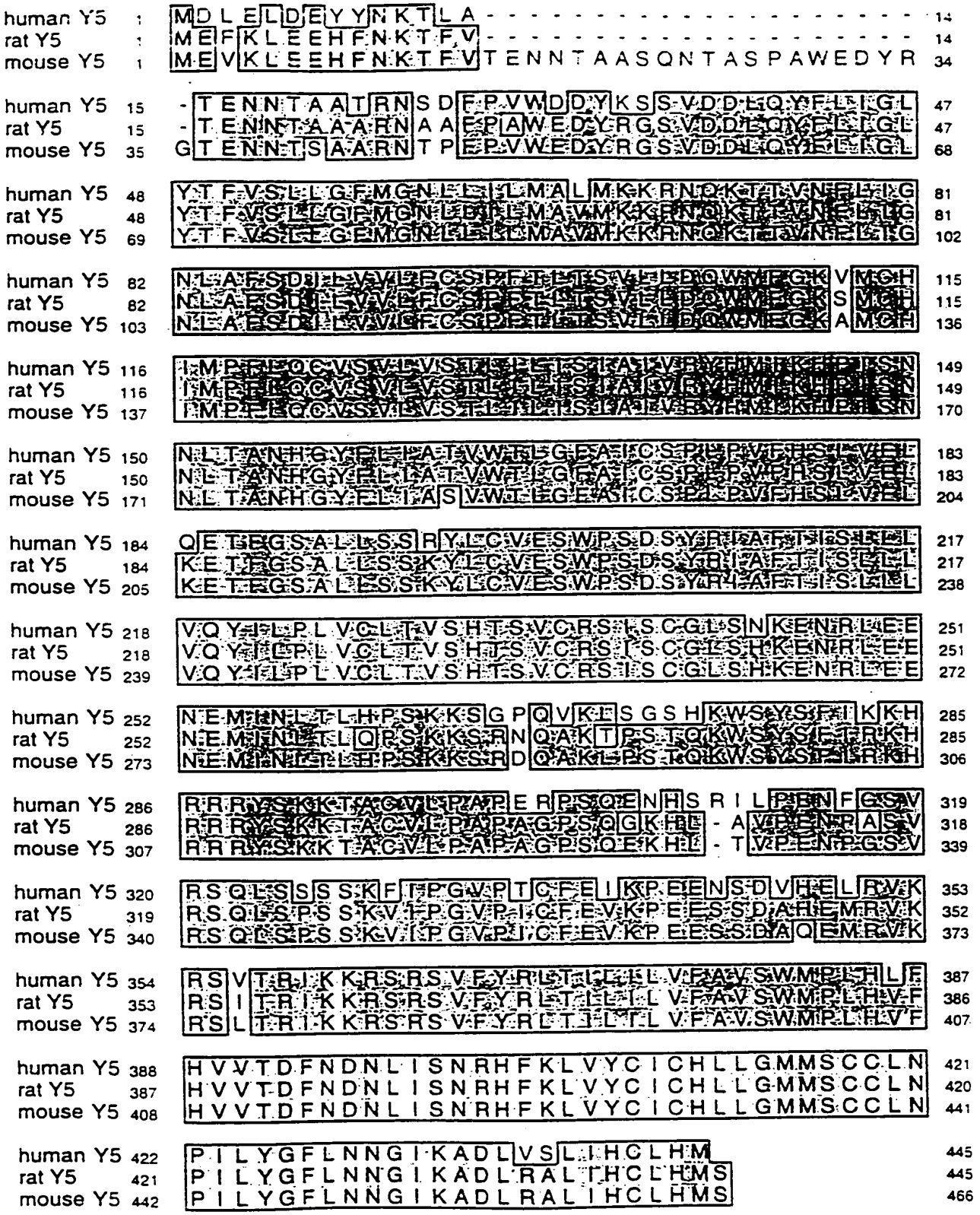

human Y5 1 MDLELDEYYNKTLA 14
rat Y5 1 MEFKLEEHFNKTFV 14
mouse Y5 1 MEVKLEEHFNKTFVTENNTAASQNTASPAWEDYR 34
human Y5 15 -TENNTAATRNSDFPVWDDYKSSVDDLQYFLIGL 47
rat Y5 15 -TENNTAAARNAAFPAWEDYRGSVDDLQYFLIGL 47
mouse Y5 35 GTENNTSAARNTPFPVWEDYRGSVDDLQYFLIGL 68
human Y5 48 YTFVSLLGFMGNLLILMALMKKRNQKTTVNFLIG 81
rat Y5 48 YTFVSLLGFMGNLLILMAVMKKRNQKTTVNFLIG 81
mouse Y5 69 YTFVSLLGFMGNLLILMAVMKKRNQKTTVNFLIG 102
human Y5 82 NLAFSDLLVVLFCSPFTLTSVLLDQWMFGKVMCH 115
rat Y5 82 NLAFSDLLVVLFCSPFTLTSVLLDQWMFGKSMCH 115
mouse Y5 103 NLAFSDLLVVLFCSPFTLTSVLLDQWMFGKAMCH 136
human Y5 116 IMPFFQCVSVLVSTLSLLTSIAIDRYHMIKHPLSN 149
rat Y5 116 IMPFFQCVSVLVSTLSLLTSIAIDRYHMIKHPLSN 149
mouse Y5 137 IMPFFQCVSVLVSTLSLLTSIAIDRYHMIKHPLSN 170
human Y5 150 NLTANHGYFLIATVWTLGFAICSPLPVFHSLVEL 183
rat Y5 150 NLTANHGYFLIATVWTLGFAICSPLPVFHSLVEL 183
mouse Y5 171 NLTANHGYFLIASVWTLGFAICSPLPVFHSLVEL 204
human Y5 184 QETEGSALLSSRYLCVESWPSDSYRIAFTISSLLL 217
rat Y5 184 KETEGSALLSSKYLCVESWPSDSYRIAFTISSLLL 217
mouse Y5 205 KETEGSALLSSKYLCVESWPSDSYRHAFTISSLLL 238
human Y5 218 VQYILPLVCLTVSHTSVCRSISCGLSNKENRLEE 251
rat Y5 218 VQYILPLVCLTVSHTSVCRSISCGLSHKENRLEE 251
mouse Y5 239 VQYILPLVCLTVSHTSVCRSISCGLSHKENRLEE 272
human Y5 252 NEMHNLTLHPSKKSGPQVKLSGSHKWSYSFIKKH 285
rat Y5 252 NEMINLTLQPSKKSRNQAKTPSTQKWSYSFITRKH 285
mouse Y5 273 NEMNNLTLHPSKKSRDQAKLPSTQKWSYSPSLRKH 306
human Y5 286 RRRYSKKTACVLPAPERPSQENHSRILPSNFGSAV 319
rat Y5 286 RRRYSKKTACVLPAPAGPSQGKHL-AVPENPASSV 318
mouse Y5 307 RRRYSKKTACVLPAPAGPSQEKHL-TVPENPGSSV 339
human Y5 320 RSQLSSSSSKFTPGVPTCFEIKPEENSDVHELRVK 353
rat Y5 319 RSQLSPSSSKVIPGVPICFEVKPEESSDYAQEMRVK 352
mouse Y5 340 RSQLSPSSSKVIPGVPICFEVKPEESSDYAQEMRVK 373
human Y5 354 RSVTRIKKRSRSVFYRLTICLLLVFAVSWMPLHLF 387
rat Y5 353 RSITRIKKRSRSVFYRLTLLTLVFAVSWMPLHVF 386
mouse Y5 374 RSLTRIKKRSRSVFYRLTLLTLVFAVSWMPLHVF 407
human Y5 388 HVVTDFNDNLISNRHFKLVYCICHLLGMMSCCLN 421
rat Y5 387 HVVTDFNDNLISNRHFKLVYCICHLLGMMSCCLN 420
mouse Y5 408 HVVTDFNDNLISNRHFKLVYCICHLLGMMSCCLN 441
human Y5 422 PILYGFLNNGIKADLVSLIHCLHM 445
rat Y5 421 PILYGFLNNGIKADLRALIHCLHMS 445
mouse Y5 442 PILYGFLNNGIKADLRALIHCLHMS 466

FIGURE 6a

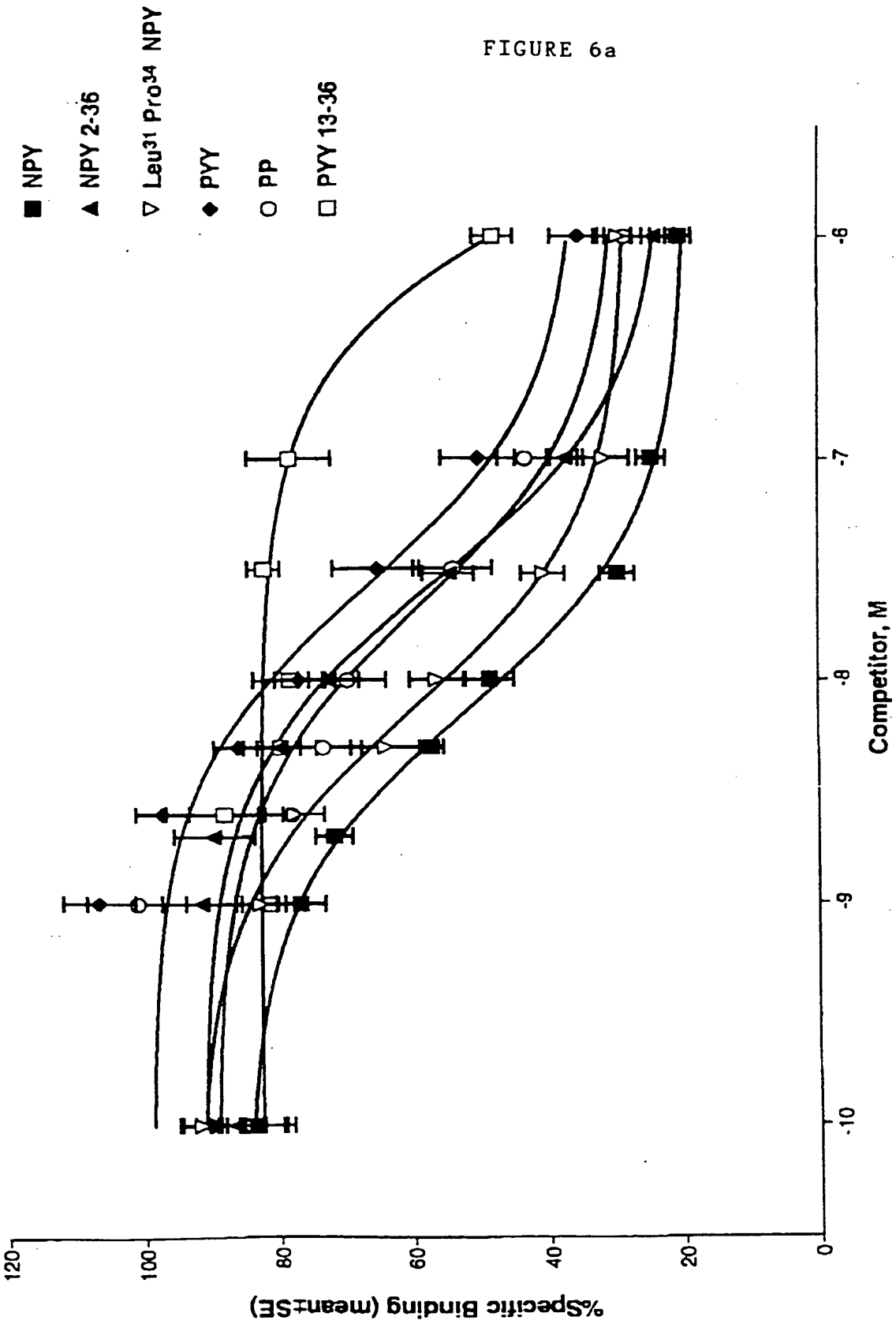

NPY
NPY 2-36
Leu31 Pro34 NPY
PYY
PP
PYY 13-36
%Specific Binding (mean±SE)
120
100
80
60
40
20
0
-6
-7
-8
-9
-10
Competitor, M

FIGURE 6b

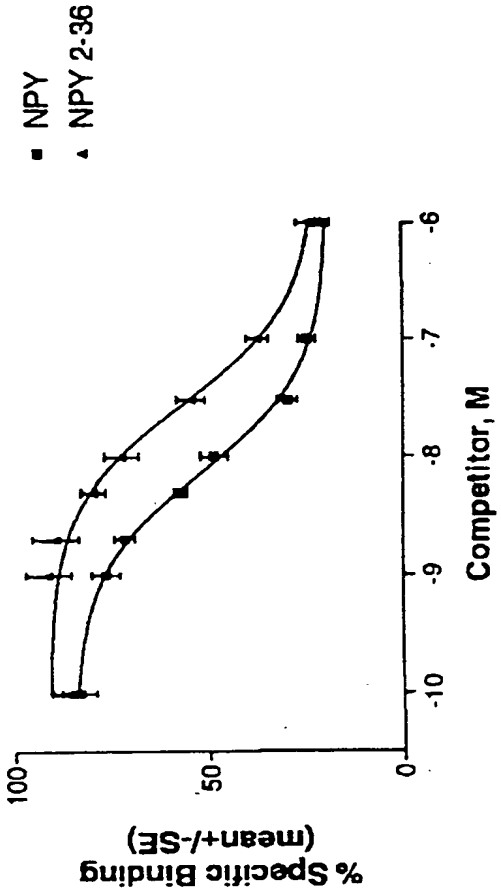

NPY
NPY 2-36
% Specific Binding
(mean+/-SE)
100
50
0
-6
-7
-8
-9
-10
Competitor, M

FIGURE 6c

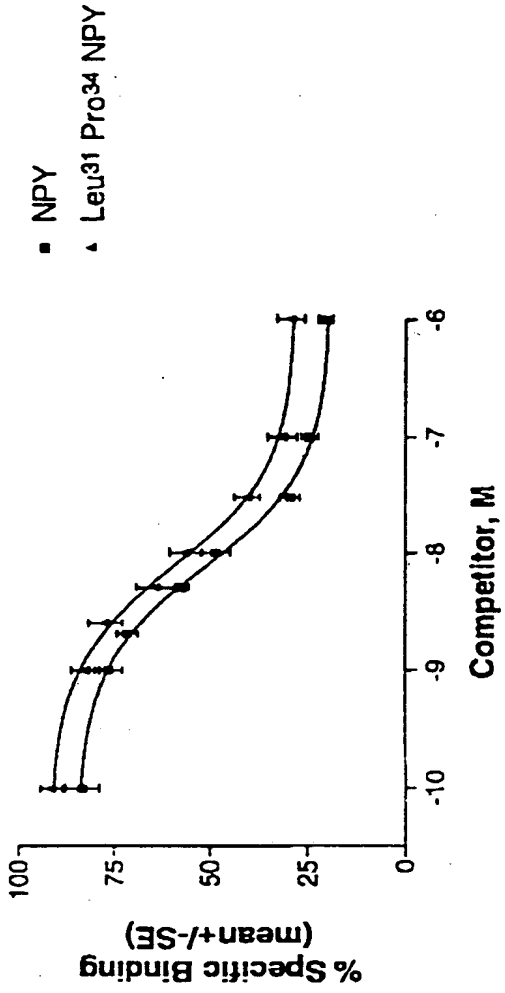

NPY
Leu31 Pro34 NPY
% Specific Binding
(mean+/-SE)
100
75
50
25
0
-10
-9
-8
-7
-6
Competitor, M

FIGURE 6d

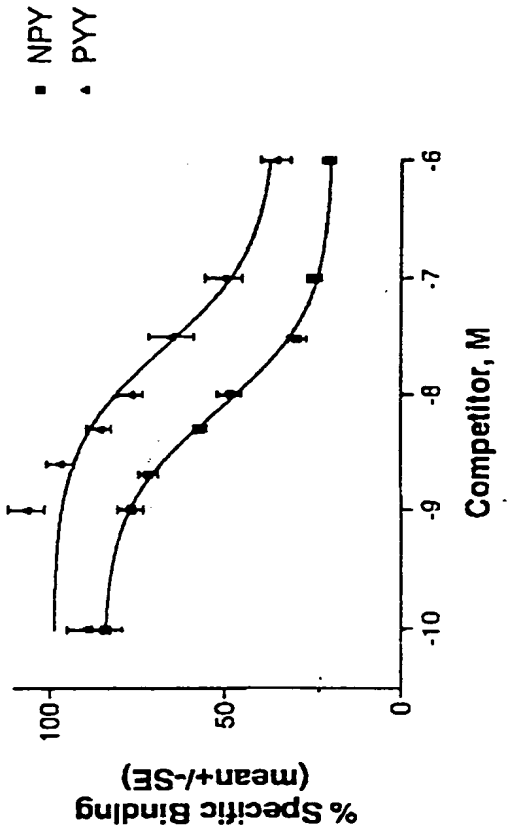
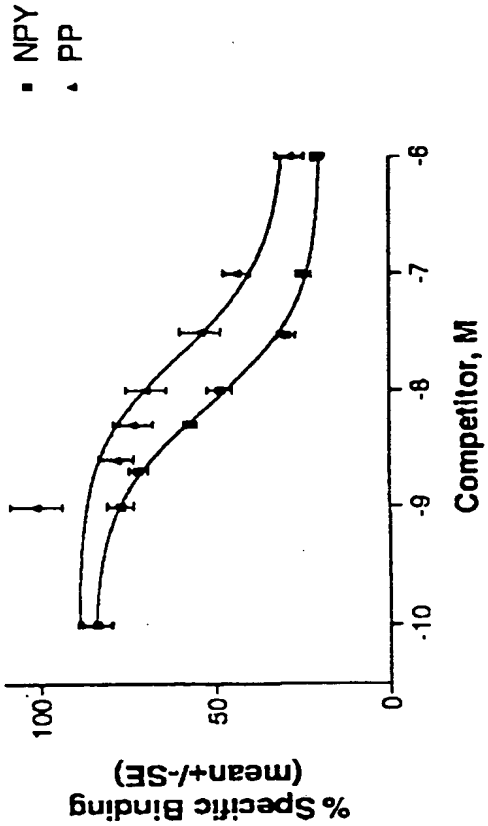

NPY
PYY
% Specific Binding
(mean+/-SE)
100
50
0
-10
-9
-8
-7
-6
Competitor, M

FIGURE 6e



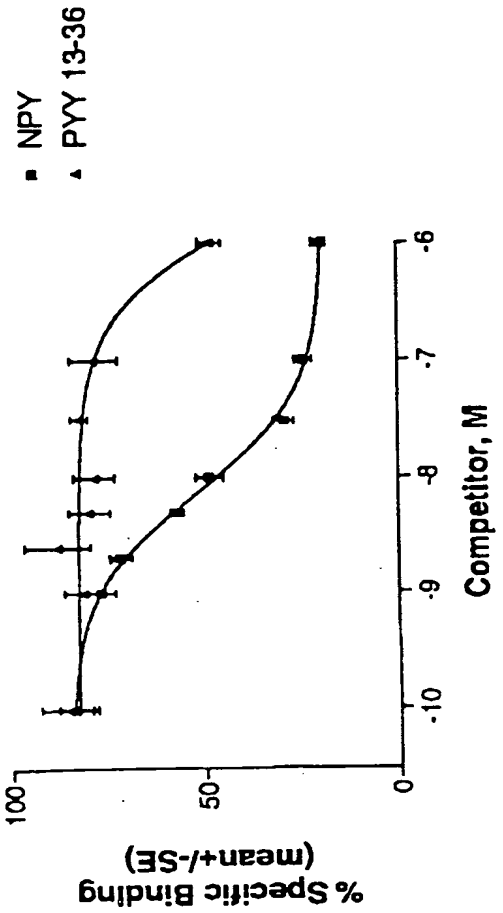

■ NPY
▲ PYY 13-36
% Specific Binding
(mean+/-SE)
100
50
0
-6
-7
-8
-9
-10
Competitor, M

FIGURE 6f

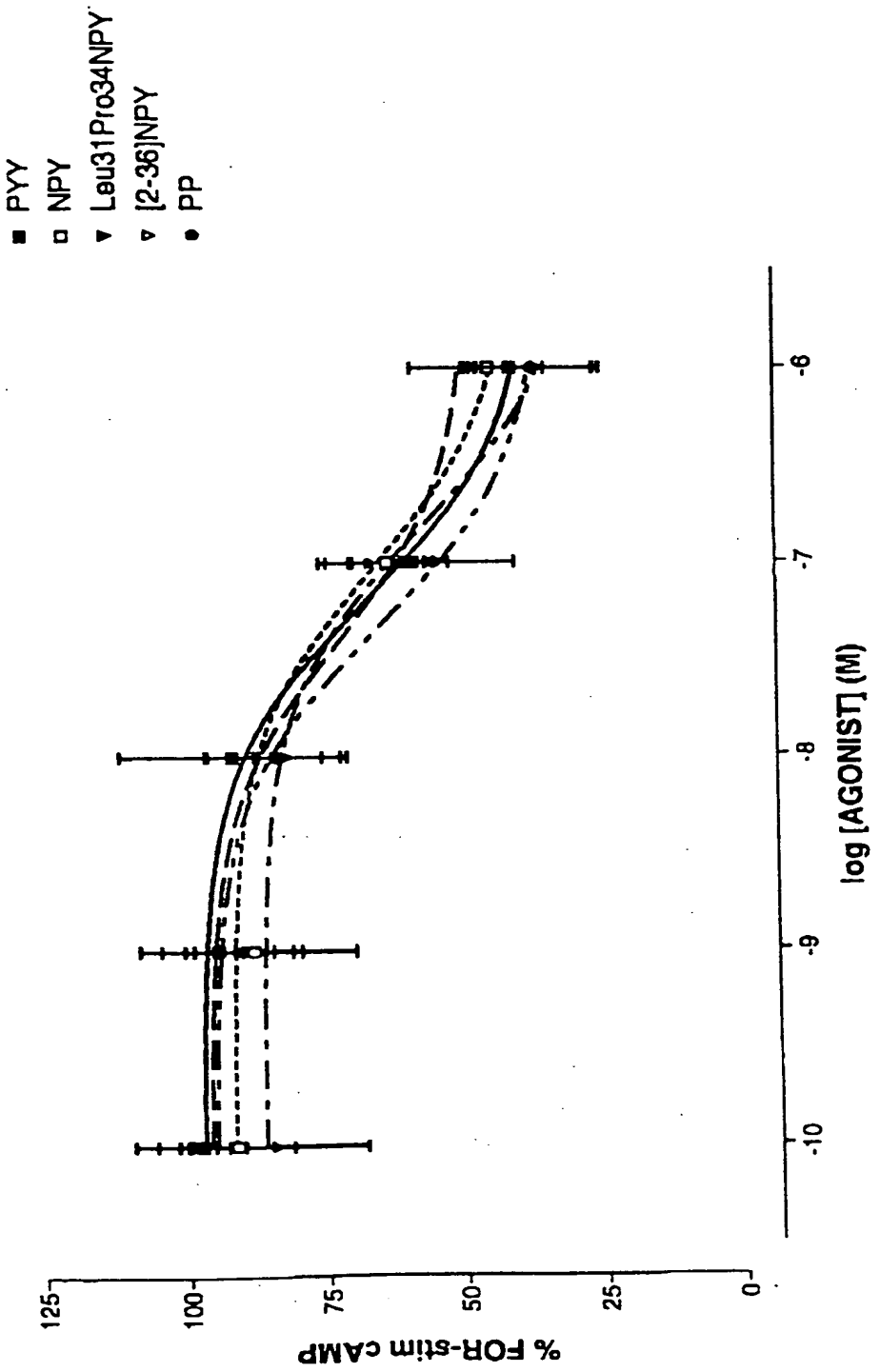

PYY
NPY
Leu31Pro34NPY
[2-36]NPY
PP
% FOR-stim cAMP
125
100
75
50
25
0
log [AGONIST] (M)
-6
-7
-8
-9
-10

FIGURE 7

# INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 96/00706

## A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: C12N 15/12, 5/10, 15/11; C07K 14/705, 16/28; G01N 33/68; C12Q 1/68

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
WPAT, CHEMICAL ABSTRACTS (SEE KEYWORDS IN ELECTRONIC DATA BASE BOX BELOW)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPM; JAPIO; MEDLINE; GENEBANK; SWISS PROTEIN

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WPAT, JAPIO,and USPM:- KEYWORDS: NEUROPEPTIDE Y RECEPTOR; Y# RECEPTOR; CHEMICAL ABSTRACTS and MEDLINE:- KEYWORDS, NEUROPEPTIDE Y RECEPTOR, Y5 RECEPTOR; following subsequences were searched on STN (CAS ONLINE): LLDQWMFGK[SVA]MCH; ENEMINLTL[QH]PSK, ATTGCTAGTTCAGTATATTCTG; ATGAATTGAGAGTAAAACGTTC; Sequences defined in claim 4 were searched on GENEBANK and SWISS PROTEIN databases.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| PX | WO 9616542 (SYNAPTIC PHARM CORP) 16 June 1996.<br>See whole document, especially examples. | 1-22 |
| PX | WO 9623809 (Merck & Co Inc) 8 August 1996.<br>See whole document, especially examples and seq id 4. | 1-22 |

[X] Further documents are listed in the continuation of Box C

[ ] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 17 February 1997 | 26 FEB 1997 |
| Name and mailing address of the ISA/AU<br>AUSTRALIAN INDUSTRIAL PROPERTY ORGANISATION<br>PO BOX 200<br>WODEN ACT 2606<br>AUSTRALIA Facsimile No.: (06) 285 3929 | Authorized officer<br><br>JIM CHAN<br>Telephone No.: (06) 283 2340 |

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 96/00706

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| PX | HU Y. et al "Identification of a Novel hypothalamic neuropeptide Y receptor associated with feeding behaviour". Journal of Biological Chemistry volume 271 (18 October 1996) pp26315-26319; see especially figures 1 and 2. | 1-17 |
| PX | Weinberg D.H. et al "Cloning and expression of a novel neuropeptide Y receptor" Journal of Biological Chemistry volume 271 (12 July 1996) pp16435-16438; see especially figure 1. | 1-17 |
| PX | Matsumoto M. et al "Inactivation of a novel neuropeptide Y/peptide YY receptor gene in primate species" Journal of Biological Chemistry volume 271 (1 November 1996) pp27217-27220; see especially figure 1. | 1-17 |
| PX | GERALD C. et al "A receptor subtype involved in neuropeptide-Y-induced food intake" Nature volume 382 (11 July 1996) pp168-171; see especially figure 1. | 1-19<br>21-22 |

**INTERNATIONAL SEARCH REPORT**
Information on patent family members

International Application No.
**PCT/AU 96/00706**

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| Patent Document Cited in Search Report | | Patent Family Member | | | | | |
|---|---|---|---|---|---|---|---|
| WO | 9616542 | CA | 2174529 | AU | 9645063 | EP | 732875 |

END OF ANNEX